CIRM Scientific Strategy Advisory Panel Meeting
February 22, 2021

Convened jointly by:
Maria T. Millan, MD, CIRM President and CEO
Jonathan Thomas, PhD JD, CIRM ICOC Chairman

Scientific Strategy Advisory Panel

Chris Austin, M.D. - Director of the National Center for Advancing Translational Sciences (NCATS) at the NIH
George Daley, M.D., Ph.D. - Harvard Stem Cell Biologist and Dean of the Harvard Medical School
Victor Dzau, M.D. - President of the National Academy of Medicine
Kevin Eggan, Ph.D. - Harvard stem cell biologist and Director of Stem Cell Biology at the Broad's Stanley Center for Psychiatric Research
Peter Marks, M.D., Ph.D. - Director of FDA-CBER
Mike McCune, Ph.D. - Senior Advisor for Global Health, Gates Foundation
Christine Mummery, Ph.D. - Professor of Developmental Biology at Leiden University Medical Center, Netherlands and President of the International Society for Stem Cell Research (ISSCR)
Bob Nelsen, M.B.A. - Co-Founder and Managing Director of ARCH Venture Partners
Derrick Rossi, Ph.D. - former CIRM Scholar, co-founder of Moderna and CEO Convelo Therapeutics
Josh Sanes, Ph.D. - Harvard neurobiologist and Professor of Molecular and Cellular Biology
Ilyas Singeç, M.D., Ph.D. - Director, NCATS Stem Cell Translation Laboratory
Sally Temple, Ph.D. - Founder, Neural Stem Cell Institute, Professor SUNY Albany
Amy Wagers, Ph.D. - Co-Chair of the Harvard Department of Stem Cell and Regenerative Biology
Fiona Watt, D.Phil. - Director of the Centre for Stem Cells & Regenerative Medicine at King's College London and Executive Chair of the UK Medical Research Council

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Background

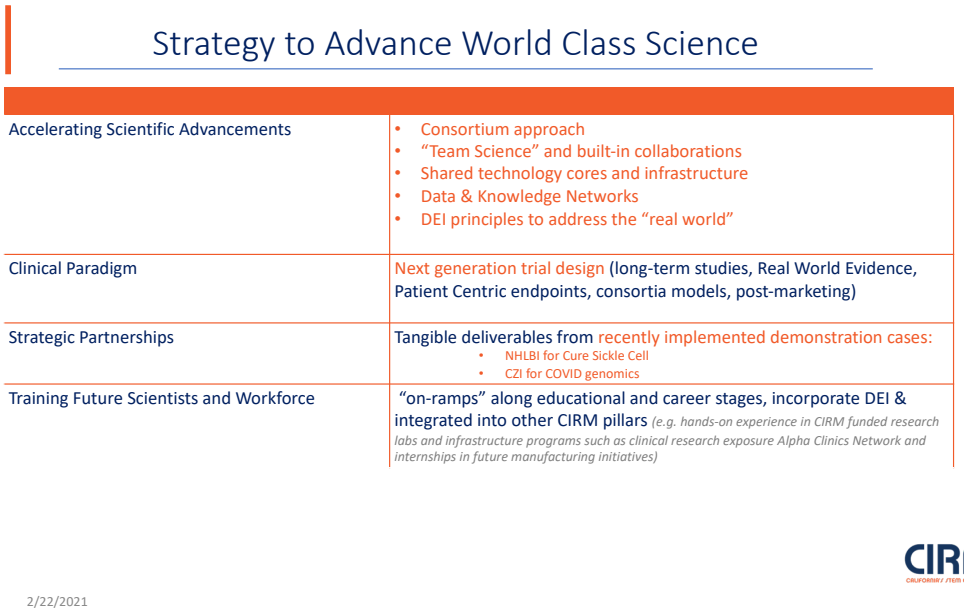
The California Institute for Regenerative Medicine (CIRM) is dedicated to the acceleration of effective treatments and cures to patients. With $5.5 billion in new funding approved by California voters in November 2020, CIRM is now poised to build on its 14-year experience and accelerate development of innovative regenerative medicine approaches and ensure equitable access to patients with unmet medical needs.

The fields of stem cell science and regenerative medicine have matured considerably since CIRM was founded in 2004 and continue to evolve rapidly. Capitalizing on technological progress in biomedical research (genomics, single-cell technologies, data analytics) and remarkable innovation within the stem cell field, major advances have brought cures to some, but many unmet medical needs are still awaiting breakthroughs in regenerative medicine.

To help position CIRM strategically for greatest impact in the next 10 years, the CIRM president and the CIRM Board chair convened a joint Scientific Strategy Advisory Panel. Key experts from academia, National Institutes of Health (NIH), the Food and Drug Administration (FDA), a foundation, and venture capital, discussed the status of the field, the persistent hurdles that need focused attention and possible near- and longer-term therapeutic goals that CIRM could pursue in light of its renewed mandate and expanded scope. As under Proposition 71, CIRM will continue to focus on research into (i) stem cell biology and cell therapies, based on human embryonic stem cells (hESC), induced pluripotent stem cells (iPSC), mesenchymal stem cells (MSC), hematopoietic stem cells (HSC), and other stem or progenitor cells, (ii) projects that use stem cells as a tool, such as disease in dish models, (iii) direct reprogramming of cells from one cell type into another, and (iv) the use of small molecule drugs or biologics if their use in research or clinical development is related to stem cells. Proposition 14 broadens CIRM's scope of research to include work related to gene therapies, whether stem cell-related or not. Proposition 14 also continues to allow the pursuit of vital research opportunities identified by the CIRM Board.

Meeting Format

To frame the conversation, CIRM president presented CIRM's strategic planning themes and anchoring questions. Then, representatives from the CIRM scientific community and Grants Working Group provided short updates on selected themes (Agenda in Appendix I), each followed by a panel discussion to identify significant opportunities to accelerate scientific advancements, ensure movement of projects along the translational and clinical development pipeline and promote innovative clinical study paradigms. The topics discussed can be broadly categorized into what scientific questions CIRM should pursue, and how it should do so.



What scientific impact can CIRM make over the next 10 years?

The discussions were framed mainly in the context of neuroscience, since Proposition 14 earmarks more than a quarter of its funds, or $1.5 billion, for research and development of treatments for brain and central nervous system diseases such as Alzheimer's disease, Parkinson's disease, stroke, dementia, epilepsy, depression, brain cancer, schizophrenia, autism, and other diseases and conditions of the brain. However, the principles discussed can be readily applied to other diseases.

The ideas that emerged have been categorized here into three main themes, (1) Harness stem cell biology to advance understanding of human diseases (2) Overcome translational barriers for stem cell and gene therapies, and (3) Extend CIRM's unique funding model to impact under-funded or emerging research areas.

I. Harness stem cell biology to advance understanding of human diseases

1. iPSC-based disease modeling

Ever since human iPSCs were first derived in 2007, countless laboratories have been pursuing their use as disease in a dish models, to gain insights into disease mechanisms, identify biomarkers for disease status, screen for drug candidates and use as preclinical models (clinical trials in a dish). To create disease in a dish models, iPSCs are derived from patient cells and differentiated into disease-relevant cell type(s). The study of monogenic diseases using iPSC models has shed light on potential disease mechanisms, and a limited number of drugs identified using iPSC-based models have been and are currently being tested in clinical trials.

Rare forms of Alzheimer's disease, Parkinson's disease and Amyotrophic Lateral Sclerosis are caused by specific mutations, and iPSC models derived from such patients have advanced our knowledge of disease mechanisms. Sporadic disease is much more common though, and if iPSC models could yield information about valid targets for therapy development and disease subtypes, they could have a tremendous impact. However, attempts to identify disease-relevant readouts in iPSC derived from patients with sporadic neurodegenerative disease have been disappointing so far.

1a. Enabling large scale iPSC-based studies of complex diseases

Sporadic diseases are complex, caused by the interaction of multiple genes with environmental and lifestyle factors, and it remains largely unknown which disease characteristics are maintained through the iPSC derivation and differentiation process. iPSC models from a large number of patients (1000s) will need to be analyzed to detect relatively weak signals of disease. Such large-scale studies are complicated by inherent differences among iPSC, as genetic variability is known to affect reprogramming efficiency and iPSC differentiation potential. Most importantly, though, reproducible protocols for the derivation, propagation and differentiation of iPSC are absolutely critical to keep the technical variability at a minimum. Panelists stated that the iPSC differentiation process needs to be automated, miniaturized and scaled for successful large-scale studies of sporadic neurodegenerative diseases. Set-ups that allow continuous microscopic imaging, rather than moving cells in and out of incubators to record readouts, also

reduce experimental variation. (NCATS's Stem Cell Translation Laboratory (SCTL) develops and shares protocols for iPSC-based research.)

Other important advances needed to enable large scale studies for the detection of relatively weak signals include increasing the efficiency of differentiation, and the development of molecular readouts that are more sensitive than current assays.

1b. Authenticity of cell type and disease readout

Successful disease modeling using iPSC critically depends on faithfully mimicking relevant aspects of *in vivo* disease pathology. Funding is needed to improve and validate the authenticity of iPSC-derived differentiated cell types, using human fetal tissues for comparison. There is also a critical need for the development of disease-relevant assays, including sensitive imaging and proteomics modalities.

Two cell technologies hold great promise to address some of these issues. Under appropriate conditions, iPSC form organoids, which are self-organized three-dimensional structures that mimic some of the characteristics of an organ. They consist of multiple cell types and better represent organ structure and function than monolayer cultures. Similarly, cells differentiated from iPSC can be incorporated into tissue chip devices that are designed as miniaturized models of organ structure and function and can be readily deployed in automation. As mentioned above, it is key that the authenticity of the iPSC-derived organoids and tissue chips and the disease relevance of the readouts is validated.

1c. iPSC-based drug discovery

In addition to informing disease biology, iPSC-based approaches may also be used in drug screens, using e.g., disease-specific cell lines. The discussion focused on screening on organoid models, which can be scaled to screen thousands of compounds, using omics and high content imaging readouts. This allows the use of, e.g., a 14,000-compound library, funded by the Bill & Melinda Gates Foundation, that includes nearly all small molecules that have reached clinical development or undergone significant preclinical profiling, so their pharmacology and safety profiles are already known. Unique opportunities, not much pursued by pharma, include the discovery of small molecules with regenerative effects.

2. Disease mechanisms

Panelists discussed that one of the main reasons progress has been slow, and clinical trials have failed so far for neurodegenerative and neurodevelopmental conditions, is our rudimentary understanding of the mechanisms of disease. The study of disease mechanism *per se* does not fall squarely into CIRM's mandate, unless pursued via stem cell-based modeling. Panelists felt however that broader investment in this area is essential to enable the rational development of stem cell and gene therapies.

2a. Identify bona fide targets for therapy development

The histopathology of neurodegenerative brains is well described, but without knowing the fundamental cause of disease, valid targets for therapy development cannot be identified. Important areas that need attention are studies into the very early stages of disease, which may precede dementia symptoms by years, and into the contribution of the microenvironment, non-neuronal cells such as astrocytes and inflammatory cells, as well as vascular abnormalities to neurodegenerative disease. Such knowledge would support development of ancillary treatments or bioengineering solutions to achieve better outcomes.

Unlike neurodegenerative diseases, where specific neuronal subtypes or broad neuron populations degenerate and die, psychiatric diseases are driven by abnormal connections between neurons (neural circuits), and by patient experiences (experiential factors). A missed opportunity so far has been the detailed study of developmental origins of neurodevelopmental diseases, and studies of epigenetic changes in human brains are needed to learn how experience molds the brain and how it interacts with genetics. While mouse models of psychiatric disease do not represent the human condition well, human brain organoids and chimeric animals may provide insights into pathologies of neural circuitry. Since mental disorders disproportionately affect the young, pursuit of therapies could have a substantial impact on the health of children.

2b. Subtypes of diseases

Neurodegenerative and neurodevelopmental diseases are heterogeneous, affecting a highly complex organ with ~100 billion cells and ~100 trillion connections among them. Research to develop a deeper understanding of subtypes of diseases and to identify covariates such as sex, is needed to better target therapeutic approaches to the underlying disease-causing defects. By including multiple subtypes of patients diagnosed with e.g., Alzheimer's disease in a trial, important differences among them may obscure signals of therapeutic efficacy in a subset of patients, derailing what may have otherwise been a successful clinical trial. In other words, the ability to show efficacy of a treatment may depend on selecting patients likely to benefit from a therapeutic approach based on their specific disease subtype. Also, identifying meaningful outcomes measures for clinical trials may depend on understanding subtypes of diseases.

Panelists suggested that a better understanding of the progression of disease over time, its natural history, would make important contributions to our understanding of disease mechanism and disease heterogeneity, and that racial and ethnic diversity in natural history studies is of critical importance.

2c. Reverse translation – learning from clinical trials

Parkinson's disease represents a neurodegenerative disease affecting a defined population of neurons, i.e., dopaminergic neurons, and clinical studies of cell-based therapies have resulted in limited successes with extremely variable outcomes. Studies are needed to determine why patients respond differently to treatment, and biomarkers for disease progression and therapy response need to be developed and validated. There is also a need for better cell delivery techniques that may include robotics in the operating room.

To learn from clinical trials, CIRM could fund data-driven meta-analyses, to improve statistical power where possible, and to uncover otherwise hidden information about trial outcomes and

why some trials worked better than others. Panelists also emphasized the importance of following patients who participated in stem cell or gene therapy trials over long periods of time, to understand long-term outcomes and heterogeneity in response to treatments. CIRM could seek an international alliance for a patient registry and central data repository, similar to the Center for International Blood and Marrow Transplant Research (CIBMTR).

2d. Emerging clinical needs

Panelists pointed to emerging clinical needs that may represent opportunities for regenerative medicine approaches or "disease in a dish" models. They included psychiatric deficits that are observed in some patients after COVID disease, and the effects of narcotics on young adult brains.

II. Overcome translational barriers for stem cell and gene therapies

1. Maturation of stem cell-derived therapies

The stem cell field has matured considerably, bringing the treatment of some diseases into the clinic but for many others the development of therapies remains in its infancy. Panelists highlighted persistent challenges in translational cell therapy research where CIRM support could greatly improve the likelihood of success.

1b. Human pluripotent stem cell (hPSC) differentiation and manufacture

hPSC-based therapy development critically depends on reproducible differentiation of hPSCs, and strong efforts are still needed to improve this process. Specific manufacturing processes, product characteristics, and product testing must be defined in order to ensure that the product is safe, effective and consistent between batches (CMC, chemistry, manufacturing and control). Automation and systematization of processes and data are needed to create a robust cell manufacturing process.

> "It is not so much about what could we do, we could do almost anything. The question is what do we have to do to get these technologies to patients?"

In order to be able to scale cell manufacturing, innovation is needed to make the process better, faster and cheaper. Research into the fundamental principles of robust cell manufacturing processes is not typically funded by the NIH, and CIRM can have a unique impact, not only by advancing stem cell therapies but also through economic return. Production patents, more so than composition patents, support most of private sector investment.

It is also of critical importance that the authenticity of hPSC-derived differentiated cell types is validated. *See section I.1b. for more detail.* A related challenge is our limited knowledge of the stage of differentiation that is optimal for transplantation of hPSC-derived cell products.

1c. Immune response

Without elaborating, panelists pointed to the continued need to address immune responses to transplanted cells.

2. Cutting edge opportunities at the intersection of stem cell and gene therapy: in vivo gene therapy and gene editing

Significant progress in gene therapy has led to cures for monogenic diseases such as severe combined immune deficiency (SCID), sickle cell disease (SCD) and beta-thalassemia. Gene therapy can also be used to genetically alter cells for other therapeutic purposes. For instance, the FDA has approved the use of genetically altered T cells (CAR-T cells) for the treatment of B cell lymphomas. These gene therapies involve the removal of HSC or T cells, respectively, from the patient, followed by genetic modification *ex vivo*, and re-infusion of genetically altered cells into the patient. While curative, this approach is extremely laborious and expensive and will therefore not likely become available to most patients. One of the opportunities that generated a lot of enthusiasm among panelists, where CIRM could have an enormous impact, is the development of *in vivo* gene therapies: a gene vector is directly injected into patients, circumventing the need for *ex vivo* cell manipulation. This would democratize gene therapies, making it possible to bring, e.g., a gene therapy cure for SCD to large numbers of African Americans and people in sub-Saharan Africa, where the disease is most prevalent.

Gene therapy for monogenic diseases

The FDA has approved gene therapy products for the treatment of RPE65-mutation-associated retinal dystrophy and SMN1-mutation-associated spinal muscular atrophy, while gene therapy for SCID, SCD and beta-thalassemia has been shown to be successful and is currently available in a research setting. CIRM was a major supporter of Donald Kohn's work to cure SCID and has been collaborating with the NIH on supporting the work to cure SCD.

Gene therapy to alter cells for therapeutic purposes

The FDA has approved gene therapy products for the treatment of certain B cell lymphomas, in which autologous T cells are transduced with a gene encoding CD19-directed chimeric antigen receptors (CAR-T cells). This represents an example of introducing a genetic product into a cell to change the cell's behavior, in this case program T cells to specifically target cells expressing CD19 for killing. Other examples, funded by CIRM, include studies in which stem cells are altered to overexpress neurotrophic factors like GDNF or BDNF, and then injected into animal models to slow the progression of neurodegenerative diseases like Huntington's disease and amyotrophic lateral sclerosis. Similarly, CIRM funds work by Sangamo to interfere with the expression of a gene called CCR5 in T cells. In people infected with HIV, this can prevent the virus from being able to enter T cells, thereby affecting a functional cure. In vivo reprogramming to replace lost cells by converting other nearby cells to the desired cell type would also fall into this category of gene therapy.

In gene therapy, a piece of DNA is added to a cell and it either randomly integrates into the genome or persists in an extrachromosomal state. Another scientific breakthrough with enormous therapeutic potential is a gene editing technology called CRISPR-Cas9 (CRISPR for short), which allows precise alteration of the genome at a specific location. If gene therapy and gene editing can be performed *in vivo*, scientists can begin to envision affordable therapeutic approaches for many diseases, but considerable research and development efforts will be needed.

Panel members commented that CIRM should focus on the intersection of gene therapy and stem cells / regenerative medicine and CIRM should pick indications where gene therapy could serve large patient populations as well as orphan and rare indications. One of the presenters made the case that some efforts, especially in the ultra-rare or rare indications, may only be achievable in academic centers and networks because they may not fit into industry model.

2a. More likely to succeed versus hard problems

One discussion centered on whether CIRM should pursue *in vivo* gene therapy projects with highest probability of success, where proof of concept in humans already exists from *ex vivo* gene therapies, or for organs that are more easily targeted, such as skin and eye. Alternatively, should CIRM pursue hard problems, such as *in vivo* gene therapy treatments to combat complex neurodegenerative and neurodevelopmental diseases. Comments were made in favor of both, and it may be prudent to pursue both. Projects more likely and more quickly to succeed could have a tremendous positive impact on the public's perception of CIRM's work, but such projects are also less likely to benefit from CIRM support, since such efforts are already well funded by others. Given CIRM's size and mandate, the agency is poised to, and should, tackle big problems to bring solutions for intractable problems affecting large patient populations. It was also mentioned that even the more mature approaches are still in need of much research and development and cannot be considered easy wins. An important example of a relatively mature *ex vivo* gene editing approach, currently tested in clinical trials, is to genetically engineer resistance to HIV infection in HSC. If this could be accomplished by *in vivo* gene therapy / editing, the devastation caused by AIDS in Sub-Saharan Africa could begin to be addressed.

2b. Research needs for gene therapy and gene editing

Panelists pointed to several important issues that need to be addressed to accelerate development of *in vivo* gene therapy / editing approaches. A major concern remains the potential for genotoxicity, i.e., will the introduced genetic material integrate into the genome, or will CRISPR-Cas9 have off-target effects, in such a way that it causes cancer. Gene therapy companies UniQure and Bluebird reported recently that one and two clinical trial participants, respectively, developed cancer, but it is not yet known whether the cancers are linked to the gene therapy. Also, in gene therapies that introduce a new protein, as would be the case in monogenic disease patients who entirely lack a protein, an additional safety concern relates to a potential immune response against that protein.

To address important safety concerns, CIRM could support basic research that addresses the potential for genotoxic effects, through e.g., developing "in and out" approaches that allow genes introduced into humans to be turned off or be removed. Since gene editing only requires transient activity of the introduced material, the delivery of DNA-based vectors can be avoided altogether, and CIRM could fund the development of CRISPR gene editing methods that employ targeted delivery of ribonucleoprotein complexes containing the Cas9 protein and the guide RNA.

There is also an urgent need for innovative new ways to evaluate genotoxicity, since current mouse models have not proven predictive, and non-human primate (NHP) models may need to be pursued. Another issue relates to clinical studies involving children. For instance, in order for a SCD treatment to have maximum impact, infants should be treated, raising ethical issues for clinical studies that would need to be addressed.

III. Extend CIRM's unique funding model to impact under-funded or emerging research areas

1. Fund research that is currently under-funded by federal agencies, foundations and industry.

CIRM may have unique opportunities for impact in critical research areas where other funding sources are sparse or do not exist. Important areas with restricted federal funding or excluded from federal funding are research involving human fetal tissue, human embryos, human gametes, and human mitochondrial replacement. Among other approaches, human fetal tissue plays an important role in validation studies for the differentiation of hPSC. *In vitro* generated human embryos allow the study of the earliest stages of human development, with the potential to gain knowledge useful for improving assisted human reproduction and preventing implantation failure, pregnancy loss and birth defects. They also would allow researchers to investigate the effects of genetic modifications in early embryos. Human gametes enable the study of the fertilization process, possibly leading to important discoveries relevant to infertility. Mitochondrial replacement has the potential to cure rare but sometimes devastating diseases caused by mutations in the mitochondrial genome.

CIRM remains well positioned to provide platforms for policy discussions related to stem cell research. Other areas with uncertain funding opportunities include human stem cell-based embryo models and embryo chimera work. And finally, although federal restrictions on hESC research funding are no longer in effect, panelists felt that shifting political winds may reverse this in the future, and that CIRM's ability to fund hESC research provides stability to the field.

2. Potential Vital Research Opportunities

Panelists reflected on whether CIRM should stay focused on stem-cell based regenerative approaches, or whether CIRM should interpret regenerative medicine more broadly. Should CIRM e.g., support small molecule-, mRNA- or shRNA-based studies that do not involve stem cells, as long as they pursue a regenerative approach? For instance, small molecules have been discovered that expand mature cardiomyocytes or hepatocytes to potentially repair heart or liver damage, respectively. Some panelists felt CIRM should embrace a broader approach to regenerative medicine, while others advocated for CIRM to not lose its identity and stay focused on stem cell-based approaches.

As mentioned above (section I.2), panelists argued that CIRM should broadly support the study of disease mechanisms, given the urgent need in e.g., neurodegenerative and neurodevelopmental conditions. Without deeper knowledge of disease mechanism and disease subtypes, rational development of stem cell and gene therapies is not possible.

2a. Disease prevention

All will agree that preventing a disease is much preferred over treating it, and panelists entertained the idea whether CIRM could fund prevention trials. In the context of regenerative medicine, the point was made that replacing lost neurons will not necessarily address all disease manifestations. For instance, in addition to neuron loss, neuroplastic mechanisms are activated in Parkinson's disease, leading to rewiring of remaining neurons that is not necessarily beneficial to the patient. If cell therapy can successfully replace lost neurons, such maladaptive responses may

not get corrected. Early intervention could prevent cell loss and maladaptive outcomes, but prevention trials are by nature very long-term and expensive. Since the pharmaceutical industry does not pursue them, prevention trials for neurodegenerative diseases may represent an opportunity for CIRM to have great impact.

How should CIRM accelerate scientific advances?

CIRM has the resources to accelerate scientific advances through large, targeted investments, exercising its convening power, and forming strategic alliances. CIRM has focused on supporting translational research for stem cell-based therapies in the past and is committed to continue de-risking promising projects this way going forward. Panelists commented that CIRM may want to pay particular attention to the transition from late-stage academic to early-stage pharma involvement, supporting development of robust, externally validated products that are likely to attract venture capital.

> "CIRM has demanded rigor in terms of CMC, MOA, it has done a service to the stem cell therapy community"
>
> "CIRM has guided us through pre-IND, the valley of death is shallower now"

The discussions on how CIRM can best support California's stem cell and gene therapy research have been categorized here into six main areas, i.e., (6) creating core facilities, (7) creating data repositories with data sharing and knowledge networks, (8) driving regulatory innovation, (9) building consortia, (10) forming strategic partnerships and (11) enabling diversity, equity and inclusion in research.

IV. Core facilities

Core services can accelerate scientific discovery and therapy development by providing high quality, standardized approaches, tools or biological resources to stem cell and gene therapy researchers across California. They can also provide access to high-cost and highly specialized technologies, not otherwise available to researchers.

1. External validation

The panel emphasized that limited reproducibility of translational research findings represents a major roadblock in the development of stem cell therapies. Use of different research protocols and variable implementation of experiments across different laboratories precludes meaningful comparisons, and a core "Hotel CIRM California" could act almost like a contract research organization, where researchers would go to validate their findings. For instance, a cell-based validation core would consist of automated hubs for cell preparations, organoid and tissue chip production, standardized assays and outcome measures to reduce technical variability and increase reproducibility. The point was made that it is not necessarily known which methods are best at producing the most disease relevant data. An external validation core could however help develop methods and benchmark meaningful outcomes and would need to be flexible enough to adjust its methods in light of new findings in the field. Collaboration with other validation centers will also be critical to advance the field.

Similarly, a core validation center for safety and efficacy studies in mice could provide reproducible findings where different approaches and modalities can be compared head-to-head. The point was made to keep the microbiome in mind when standardizing mouse models.

While external validation may be critical for advancing the translation of stem cell and gene therapies, researchers at academic institutions are not typically incentivized to seek validation and may view such a requirement by their funder as intrusive policing of their work. Successful implementation of this concept at NCATS included a collaborative approach, where all data from innovators and validators are shared. External validation is not meant to be a test of the quality of academic research, but rather an opportunity to determine what unique approaches in a specific laboratory are important for the experiment to succeed and discover reasons for poor reproducibility. By creating such synergies, the reward for the innovator is better informed science. Panelists also pointed to the importance of external validation for attracting venture capital funding.

2. Biodistribution and functional integration of transplanted cells

One of the challenges that has hampered progress in cell-based therapies relates to the difficulty of pinpointing the reasons for clinical trial failures. To answer that question, researchers need to be able to determine whether the clinical trial interrogated the hypothesis, which includes knowing whether the transplanted cells went to or stayed in the right place to be able to test the proposed mechanism of action (MOA). Did the cells engage the target, are they alive, have they functionally integrated? Biodistribution and functional integration of the transplanted cells is studied in animal models and deceased humans, but better technologies need to be developed to follow cells in living humans. This is also true for *in vivo* monitoring of gene therapy vectors. Panelists suggested that CIRM consider establishing a biodistribution core. Biodistribution analyses in experimental models can be expensive and challenging, and a centralized service may bring economies of scale. Furthermore, such a core could also be charged with developing better *in vivo,* real time imaging modalities, for both animal models and living humans. Panelists mentioned the need for innovation in ultrafast ultrasound, PET ligand and spin labeling imaging techniques to enable repeated monitoring of tissues and transplanted cells in patients.

A related critical need is the development of biomarkers to follow the effects of cell and gene therapies in living humans. This could also be addressed by creating a core that includes services and technology development.

3. Production of clinical grade cell products and gene therapy vectors

For cells to be transplanted into patients, they need to be manufactured under current Good Manufacturing Practice (cGMP). This is an expensive and highly specialized process. Robotics and artificial intelligence approaches should be used to systematize manufacturing of clinical grade cells. By providing a cGMP cell manufacturing core, CIRM could alleviate this critical bottleneck. Similarly, a core for the production of clinical-grade vectors using good laboratory practices (GLP) would be of great service to the development of gene therapies.

4. Tissue cores
Researchers need access to precious human tissues as reference samples. They include fetal tissues to ensure differentiation of iPSCs is grounded in real biology. Another valuable tissue are brains from patients with neurodegenerative diseases from all stages of life to authenticate iPSC-based disease models. These rare samples are collected in different locations, and panelists suggested that CIRM develop a mechanism to coordinate their use state-wide, as this would greatly optimize the utility of this important resource.

5. NHP disease modeling core
A main limitation of animal models in translational research is their limited relevance to the human condition. Many mouse and other animal models of disease are not good predictors of product safety and efficacy in human, and non-human primate (NHP) models may need to be pursued for certain diseases or technologies, because of their greater relevance to human biology. This is an example where a CIRM-funded core facility could have great impact, since NHP models are expensive and require unique facilities and skills. Also, similar to the external validation core concept described above, such a facility would use standardized approaches and could collect data for head-to-head comparison of cell therapy products developed by different groups. Importantly, an NHP disease modeling core would be critical for testing genotoxicity of *in vivo* gene therapy / editing approaches, since currently used mouse models are not predictive.

V. Data repositories, data sharing and knowledge networks

Data repositories are created to support large-scale projects and consortia, or to serve the scientific community. Data sharing is an integral element, both for populating a data repository and for providing broad access to it. In data repositories that contain a diversity of data types, the creation of knowledge networks then enables new discoveries by deploying advanced computing and visualization tools that integrate and analyze across data types.

1a. Data sharing
Data sharing turns out to be a major obstacle to creating data repositories from existing data, with issues ranging from questions around data ownership, business concerns related to e.g. clinical trial data, the appropriate consenting of participants who contribute data and uncertainties about protecting their privacy, and the cost of collecting, storing and harmonizing the data. For instance, some of the panel's discussions on Parkinson's disease centered on how to better harness existing knowledge and how to learn from experience in the field, since existing data from different research and clinical studies is not comparable. Some of these issues can be more easily addressed if a data repository is created as part of a newly formed project or consortium, where standard approaches to collecting and handling data can be implemented, and ownership and consent are clarified and harmonized from the start.

Data sharing goes beyond enabling specific large scale research projects, and panelists emphasized the need to democratize data, ensuring that everyone, all researchers and also citizen scientists, have access. A set of guiding principles of findability, accessibility, interoperability, and reusability (FAIR) has been developed by a consortium of scientists and organizations to support data sharing. Panelists pointed to various examples of successful sharing of high-quality data by consortia or institutes, such as the research initiative Aligning Science Across Parkinson's Disease (ASAP) and the non-profit Allen Institute. Panelists felt that CIRM has an important role to play in enabling broad sharing of data generated through the research it funds and consortia is supports. The condition of playing should be to share.

Democratizing data
To broaden accessibility to open-source platforms, the UCSC Genomics Institute is participating in Data Biosphere, a collaborative effort to move data storage and computation on biomedical data to the cloud through the development of standard-based, interoperable software packages (containers). Data Biosphere is creating data environments for groundbreaking scientific initiatives, like NIH's All of Us Research Program, the National Cancer Institute's Genome Data Commons, and the Chan Zuckerberg Initiative's Human Cell Atlas project.

Panelists emphasized that in addition to broad access to CIRM-funded data, CIRM should also ensure that tools are put in place to allow researchers not expert in quantitative sciences and computational biology to interrogate them.

1b. From data to knowledge networks
Great examples of data sharing, developed and hosted at the UC Santa Cruz Genomics Institute, are the genome browser and other open-source genomics platforms. The UCSC Genomics Institute hosts the CIRM Stem Cell Hub as part of the CIRM Center of Excellence in Stem Cell Genomics (CESCG). It represents a knowledge network, where users can explore diverse machine learning-ready data sets created by 18 CESCG laboratories. The data are linked to the UCSC genome browser and coordinated with the Human Cell Atlas and allow users to perform metadata queries. A consortium described below (see section VII.4) would leverage this resource.

VI. Regulatory innovation

The path to regulatory approval for small molecule drugs and biologics is well understood. Stem cell and gene therapies are more complex and require different regulatory approaches. The FDA has been working with the scientific community to develop paths toward clinical trials, but further innovation is needed to accelerate progress from bench to bedside.

The panel reiterated that CIRM should continue to take a leadership role in linking innovative preclinical and clinical projects with the FDA and provide expertise and help with the necessary communication. Two examples where a concerted effort by CIRM to work with the FDA could have major impact are listed next. Panelists also stated that a continuously updated 'recipe book' for regulatory science may be of use to the stem cell and gene therapy fields, where innovative new treatments that challenge current regulatory paradigms are constantly being advanced.

1. Platform-based regulatory approvals
In order to make strides in gene therapy/editing for monogenic diseases, panelists discussed the need for platform-based regulatory approvals. There are ~ 7000 known rare monogenic diseases, and on average, each monogenic disease can be caused by ~100 different mutations, in effect raising the number of different interventions needed to ~700,000. Currently, so-called n=1 studies are being performed in academic centers, where a gene therapy intervention is designed to target the exact mutation found in a given patient (size of patient population studied is 1). The goal would be to combine data from a series of successful n=1 clinical gene therapy studies, each targeting a different mutation but all using the same gene transfer or editing approach (the platform). If gene therapy approach and data collection are standardized across n=1 studies, FDA may be able to use such a data set to consider approval for the use of that platform, even if other mutations are targeted.

2. iPSC-based preclinical models for regulatory applications
A promising use of iPSC-based models is to produce validated preclinical models (clinical trials in a dish or tissue chips) for regulatory applications, which could have an enormous impact on optimizing drug discovery and therapy development. The FDA is enthusiastic about enabling such innovative advanced manufacturing technologies, and mechanisms to engage FDA exist, such as requesting meetings with CBER Advanced Technologies Team (CATT) for technology platforms. Individual investigators or large consortia can request these meetings.

VII. Consortium approach

Consortia can be designed to tackle complex problems through large scale inter-disciplinary research. Consortia allow development and deployment of standardized protocols across all participating sites, enhancing comparability of data. They may also provide resources such as centralized production of iPSC and derived organoids, offering researchers access to technologies they do not have in-house. Existing hurdles for exchanging living reagents should be addressed though, by developing better cryopreservation protocols, and simplifying and standardizing material transfer agreements.

Cross-disciplinary consortia can leverage diversity of opinions and knowledge, and may benefit from important perspectives provided by patients, patient advocates, regulators and payers. Consortia can also play a role in enhancing training at all levels, from students to principal investigators. For consortia to be successful, the project management role is critical, coordination can be unwieldy.

1. Disease-targeted consortia
To focus needed attention on especially persistent and prevalent unmet medical needs, such as neurodegenerative and neurodevelopmental diseases and many others, CIRM can build consortia to advance specific goals. To provide context, speakers described their experiences with existing consortia, such as Answer ALS, and Stem Cells for Huntington's Disease (SC4HD), that bring together cross-disciplinary partners to advance knowledge or develop therapies for a specific disease indication.

Through collaborations at multiple clinical sites, consortia enable recruitment of large patient populations, for collecting natural history data (more than 20,000 patients internationally in SC4HD consortium) or for iPSC derivation (more than 1000 patients recruited in Answer ALS). Those cohorts can be available for follow-up studies that may be inspired by emerging discoveries, and they also represent a valuable pool of well phenotyped participants for clinical trial recruitment.

The consortium Stem Cells for Huntington's Disease (SC4HD), which seeks to develop cell therapies, has been supported by CIRM in several ways. A CIRM conference grant helped initiate its founding, UCI's CIRM Alpha Stem Cell Clinic plays a critical role, and valuable interactions with members of CIRM's scientific team have helped with navigating preclinical research and interactions with the FDA.

2. Consortia based on disease area, common biological mechanism or technology platform
In addition to targeting specific diseases, consortia can be formed to exploit other synergies. Rational therapy design targets the biological mechanisms that drive disease. Such mechanism may be shared among different diseases, such as disturbances of the microenvironment, vascular abnormalities, tissue remodeling that is inhibitory to regeneration (fibrosis / scarring), inflammation or common neurodegenerative pathways. Since treating a complex disease may require a diversity of approaches, by focusing on a biological mechanism, a consortium may bring new therapeutic advances to a host of diseases.

Another concept that generated enthusiasm were platform-based consortia, where the common goal revolves around pursuing specific cutting-edge approaches or technologies for disease therapies, such as a consortium for CRISPR cures. Such a consortium could leverage learnings from targeting different diseases with CRISPR-based gene editing or gene therapy approaches and could also work strategically toward needed regulatory innovation (see section VI). A potential partner for brining n=1 therapies to patients would be the Bespoke Gene Therapy Consortium (BGTC) at the Foundation for the NIH (FNIH).

3. iPSC-based disease modeling consortia
Panelists expressed enthusiasm about a concerted effort by CIRM to support modeling of sporadic neurodegenerative and other common and complex diseases using iPSC-based technologies. They argued that a consortium approach would be required, given the large numbers of patient-specific iPSC lines that would need to be analyzed, and the cell technology advances and automation that would need to be developed and implemented (see section I.1). This is expensive, but return on investment would likely be great, and CIRM support could have a big impact if relevant disease targets and molecular disease subtypes emerge.

Panelists pointed to other organizations, such as NIH's National Center for Advancing Translational Sciences (NCATS), the New York stem Cell Foundation (NYSCF) and the Allen Institute who have embarked on large scale iPSC-based modeling, where collaborations and strategic partnerships could be formed for maximum impact.

4. Understanding human biological diversity through genomics and iPSC modeling
The UCSC Genomics Institute participates in the Human Pangenome initiative which is cataloging unbiased genome variation for clinical practice. The goal is to create a complete

reference of human genetic diversity, to overcome the current limitation of using a single human's genome as a reference in clinical practice.

The panel suggested that the generation of an iPSC line for each genome included in the Human Pangenome project was an opportunity for an impactful CIRM contribution. The panel was also enthusiastic about the possibility of leveraging CIRM's iPSC repository, contributing disease-specific or control genomes, which already have an iPSC line associated with them, to the Human Pangenome collection. Since the iPSC lines residing in CIRM's iPSC repository have already been genotyped using single nucleotide polymorphisms (SNP), specific genetic ancestries could be targeted for inclusion. Possible iPSC donor consent issues were acknowledged.

> CIRM's iPSC repository contains more than 2500 iPSC lines, derived from participants with neurodevelopmental disorders of children (epilepsy, autism, cerebral palsy), idiopathic pulmonary fibrosis, viral hepatitis, nonalcoholic steatohepatitis, cardiomyopathies, Alzheimer's disease, blinding eye diseases, and healthy control

Panelists proposed that CIRM could establish a consortium that marries iPSC technology with genomics and multi-omics approaches to systematically interrogate associations between biological and genomic variations, using large numbers of samples. Gene transfer / editing and small molecule approaches in organoids could be used to test mechanistic hypotheses generated by the association studies, and standardized and automated organoid production would ensure that technical variability is kept at a minimum. This would generate an enormous amount of data that could be organized into a knowledge network, available to everyone for further analyses.

The panel suggested that CIRM convene a workshop that would bring together potential consortium participants, including data experts (e.g., CIRM's Stem Cell Hub, Human Pangenome, Data Biosphere), representatives from existing iPSC collections (e.g., CIRM iPSC repository, Answer ALS, NCATS, NYSCF, European efforts) and other needed expertise (such as standardization, automation, organoid production, gene transfer / editing technology, omics, computation). Workshop participants would develop concepts for a possible consortium that would have as its goal to interrogate the connections between human genomic diversity, biological variation, and underlying molecular mechanisms.

VIII. Strategic partnerships

Panelists indicated that $1.5 billion to advance treatments for brain and central nervous system diseases is not enough to tackle such an enormous task. Strategic alliances are critical to solving big problems and achieving highest impact of existing resources. CIRM is already collaborating with several organizations and pursuing additional alliances (CIRM-NHLBI Partnership in the Cure Sickle Cell Initiative and the CIRM-CZI MOU for COVID programs and single cell analysis). Relevant organizations mentioned throughout the meeting included NCATS, Chan Zuckerberg Initiative (CZI), Allen Institute, Bill & Melinda Gates Foundation, Aligning Science Across Parkinson's Disease (ASAP), GForce-PD, FNIH, and the California Initiative to Advance Precision Medicine (CIAPM).

An example of an impactful international alliance CIRM could develop (see section I.2) is a patient registry and central data repository to longitudinally follow patients treated with stem cell and gene therapies, similar to the Center for International Blood and Marrow Transplant Research (CIBMTR).

IX. Diversity, equity and inclusion

CIRM is committed to developing Community Care Centers of Excellence (CCCE), which are sites that conduct human clinical trials, treatments, and cures in more remote and rural areas of California. The goal is to provide medically underserved populations with the opportunity to be included in the discovery and implementation of stem cell and gene therapies. Strategies for the development of CCCEs will be the subject of another strategic advisory panel meeting.

The principles of diversity, equity and inclusion must be applied broadly across the entire spectrum of biomedical research. Panelists commented that diversity requirements in basic research would contribute to reducing health disparities, by reversing the underrepresentation of certain racial and ethnic groups in e.g., genomic and other biomedical data sets. Similarly, efforts should be made to include children, the elderly and other underrepresented populations in human studies. Applicants to CIRM programs are already required to provide a plan for the inclusion of a diverse group of participants and must explain how the principles of diversity, equity and inclusion are embedded in their research. However, intentions for diverse participant recruitment are often met with difficulties, and CIRM could develop a program that supports its grantees in achieving these diversity goals. An example would be to target messaging of the importance of health challenges to diverse communities.

In order to gain the trust of underrepresented communities, members of those communities have to be engaged early in the discovery and development process. As an example, in the context of developing a functional cure for HIV with *in vivo* gene therapy/editing, panelists pointed to the opportunity this would create to treat HIV-infected people in sub-Saharan Africa. A concern though is that populations of color may not be receptive to such a treatment, and disadvantaged communities that may benefit from advanced therapies should be engaged early in the therapy development process.

Panelists stated that CIRM should recruit the best stem cell and gene therapy scientists to California through e.g. matching funds with recruiting institutions, and create a fellows exchange program to attract out of state fellows to the state. Another important step toward diversity, equity and inclusion would be for CIRM to create mechanisms that attract and support underrepresented minorities in the research pipeline, including at the faculty and leadership levels.

Appendix I

CIRM Scientific Strategy Advisory Panel Agenda
February 22, 2021

10 Min	7:00-7:10	JT	Intro to CIRM & Purpose
10 Min	7:10-7:20	MM	Purpose of Meeting and Agenda Design
15 min	7:20-7:35	Gil	Portfolio Overview
5 Min.	7:35-7:40	Panel	Questions
10 Min	7:40-7:50	Amander Clark	Needs in Basic research for ESC, iPSC Tech, & CNS Research
15 Min	7:50-8:05	Panel	Discussion
10 Min	8:05-8:15	Clive Svendsen	iPSC Tech for Therapeutic Development and Role of Academic GMP Facilities
15 Min	8:15-8:30	Panel	Discussion
10 Min	8:30-8:40	Claire Henchcliffe	ESC and iPSC for Parkinson's. Infrastructure Needs; Value of Networks
15 Min	8:40-8:55	Panel	Discussion
15 Min	8:55-:9:10	Leslie Thompson	Translational research for Neurodegenerative Disease. Role of natural history studies and lessons learned form the Answer ALS Consortium
15 Min	9:10-9:25	Panel	Discussion
10 Min	9:25-9:35	Patrik Brundin	New Paradigms for CNS research
15 Min	9:35-9:50	Panel	Discussion

10 min	9:50-10:00		**BREAK**
10 Min	10:00-10:10	Doug Kerr	Industry Perspective: why so few products for CNS/rare dis; Gene therapy for CNS
15 Min	10:10-10:25	Panel	Discussion
15 Min	10:25-10:40	Fyodor Urnov	Gene Therapy. Experience with CIRM CRISPR CAS9 Sickle Cell Program
15 Min	10:40-10:55	Panel	Discussion
15 Min	10:55-11:10	David Haussler	Genomics Knowledge Network
15 Min	11:10-11:25	Panel	Discussion
15 Min	11:25-11:40	Pete Schultz	Small molecule for Regenerative Medicine
15 Min	11:40-11:55	Panel	Discussion
15 Min	11:55-12:10	Cat Jamieson	Regenerative Medicine Approaches for Cancer; Alpha Clinics Network
15 Min	12:10-12:25	Panel	Discussion
35 min.	12:25-1:00		**LUNCH**
1.5 hours	1:00-2:30	Panel	*Closed Session* Report Development
30 Min	2:30-3:00	Panel	Wrap up and Report Back